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EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/678,765	SERBEDZIJA ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2007 and 29 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,33 and 35-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,33 and 35-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/02/2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's reply dated 11/16/2007 and 11/29/2007 have been received. It is noted that Applicant's reply dated 11/29/2007 was originally submitted 08/20/2007 and is treated as having been received on that date. Thus, the claims dated 11/29/2007 precede those dated 11/16/2007. The claims dated 11/16/2007 are currently under consideration. Claims 1-30,32 and 34 have been cancelled. Claims 31,39 and 40 have been amended. Claims 39 and 40 were added in the amendment received 11/29/2007 and claims 41-49 were added in the amendment dated 11/16/2007. Claims 31,33 and 35-49 are pending and under consideration in the instant office action.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) was denied as set forth at page 4 of the office action dated 08/03/2006. The effective filing date granted for the claims is 02/22/1999 based on support in US Application 09/255,397. '783 does not provide support for screening compounds by assaying for gene expression changes. Applicant has remarked that the issue of priority does not currently appear to be material to the grounds of rejection raised and will further address the issue if it becomes relevant in future proceedings.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

Claims 31,33 and 35-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening an agent for toxic activity comprising administering an agent to a teleost in vivo, processing in vitro or in situ said embryo in a manner to detect expression of a protein or mRNA in a specific organ or tissue, and quantifying mRNA or protein expression, wherein a change in said mRNA or protein expression in comparison to that of a control teleost embryo not administered the agent is indicative of toxic activity of the agent, does not reasonably provide enablement for screening an agent for a therapeutic activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Applicant has amended claim 31 to include, in addition to screening for toxic activity of an agent, screening for desired activity of the same agent in the same fish. The specification does not provide

enabling teachings and guidance necessary to know how to carry out screening for a desired therapeutic activity. Applicant points to the specification at page 31, lines 24 and 25 and page 65, lines 7-21 in support of the claim amendment. Page 31 recites that the method is useful in identifying contra indications to therapeutic value of a compound. This indicates that a known therapeutic agent is being screened for toxic effects. It does not support screening an agent for a therapeutic effect (note, this appears to be the subject matter of US 6,656,449). The specification does not support the concomitant screening of an agent for a therapeutic and toxic effect. To screen for a therapeutic activity, a disease state to be remedied or an effect of the agent to be screened must be known. The specification does not teach what activity is a desired activity or how to screen for such an activity. The claims are drawn to use of a wildtype teleost. It is not known how to screen for a "therapeutic" agent a normal, wild-type teleost. Page 65 discusses screening for both desired and undesired effects of an agent, however, the focus, again, is on screening for toxicity or undesired effects. Lines 16-21 refer to the toxic effects of drugs. It appears that the support in the specification regarding the combination of desired and toxic effects of an agent are drawn to screening the toxic effects of agents known to have a desired effect and are not drawn to screening for a desired effect. It is noted, that "desired" is not defined by the specification and encompasses any activity, including toxic activity.

Claim 31 has been amended to recite a method of screening an agent for toxic activity and a therapeutic activity comprising a step of administering an agent to a teleost, a method step of detecting a change in a teleost that is indicative of toxic active, followed by a step of "assessing whether the agent is effective to promote the therapeutic activity in the teleost". However, the claim fails to recite how such an assessment should be carried out to determine whether an agent is effective to promote a therapeutic activity. It is not known what "effective to promote the therapeutic activity" encompasses (see rejection under 35 USC 112, 2nd paragraph, below). Applicant refers to page 19, lines 13-15 and page 65, lines 10-13 in support of the therapeutic activity of the claims. However, these excerpts are merely descriptive and

are not enabling as they do not set forth or provide any guidance with respect to what characteristics would define an agent as therapeutic when administered to a normal, wildtype or otherwise healthy teleost. Page 65 of the specification discusses screening for both desired and undesired effects of an agent, however, the focus, again, is on screening for toxicity or undesired effects. The specification focuses on screening for toxic effects of known therapeutics and in this sense, when a therapeutic is given to a teleost to be treated for a disorder or disease, the therapeutic effect can be observed concomitant with screening for any potential toxic effects. The specification does not provide the guidance necessary to assess whether the agent is effect to promote a therapeutic activity.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejection of claims 31,33,35-38 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of Applicant's amendments to the claims.

The following new rejection is necessitated by amendment.

Claims 31,33,35-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "effective to promote the therapeutic activity" in claim 31 is unclear. The preamble is drawn to "A method of screening an agent for...a therapeutic activity" and the methods require "assessing whether the agent is effective to promote the therapeutic activity....". It is unclear that the phrase "effective to promote the therapeutic activity" encompasses and how that relates to screening an agent for

actually having a therapeutic activity in itself. To promote a therapeutic activity is not commensurate in scope with having a therapeutic activity. Claims 33 and 35-40 depend from claim 31.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 31,33 and 35 under 35 U.S.C. 102(b) as being anticipated by Mizell [1997, IDS] is withdrawn in light of Applicant's amendments to the claims. Claim 31 has been amended to replace the term "desired activity" with "therapeutic activity". Mizzell did not teach screening for a therapeutic activity.

1) Claims 42-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Mizell [1997, IDS].

As set forth above, priority to US provisional applications 60/075,783 and 60/100,950 for the instantly claimed subjected matter has been denied. The effective filing date is 02/22/1999.

Claim 42 is drawn to a method of screening an agent for toxic activity in vivo comprising administering an agent to a teleost and detecting a change in expression of a protein in a specific organ or tissue of the teleost, a response in the teleost indicating toxic activity in the tissue. Claim 43 requires that toxic activity be detected over time. Claim 44 requires that the response be detected in at least two tissues. Claim 45 requires that the response is over time at predetermined intervals. Claim 46 requires simultaneous testing of at least 2 teleosts.

Mizell taught a method for screening an agent for toxic activity in both zebrafish and medaka, which are teleosts that have a chorion. Mizell taught administering the agent (TCDD, toluene, benzene) to multiple (claim 46) dechorionated zebrafish embryos and detecting toxic effects by monitoring CYP1A activity (see page 416, last paragraph-page 416, paragraph 2, page 419, col. 2, paragraph 2; see Table 5, line 2 at page 96 of the specification). Early activation of CYP1A was shown as an indicator of TCDD toxicity. Multiple embryos were assayed at a time (page 421, col. 2, paragraph 4), meeting the limitations of claim 46. Mizell taught that toxic activity is detected after a 30 minute exposure to TCDD (page 415, col. 2, paragraph 2), which constitutes detecting toxicity over time at a predetermined interval as required by claims 43 and 45. Mizzel observed changes in heart formation as well as Cyp1A activity in both the gut and liver, fulfilling the limitations of claim 44.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 36-38 under 35 U.S.C. 103(a) as being unpatentable over Mizell (1997) as applied to claims 31-35, and further in view of Terse [1993, Toxicon, 31:913-919] is withdrawn in light of Applicant's amendments to the claims. Claim 31 has been amended to replace the term "desired activity" with "therapeutic activity". Mizzell did not teach screening for a therapeutic activity.

1) Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mizell (1997) in view of Maccubbin (1986, Aquatic Toxicology, 9:277-286) or Black (1988, Aquatic Toxicology, 11:129-142) or Marty *et al*, (1990, Aquatic Toxicology, 17:45-62).

Claim 41 is drawn to a method of screening an agent for toxic activity in vivo comprising administering an agent to a teleost *with a chorion*, and detecting a change in expression of a protein in a specific organ or tissue of the teleost, a response in the teleost indicating toxic activity in the tissue.

As set forth above, Mizell taught a method for screening an agent for toxic activity in teleosts. Mizell taught administering toxins to zebrafish embryos and detecting toxic effects by monitoring CYP1A activity as an indicator of toxicity. Mizell taught use of dechorionated embryos and did not teach leaving the embryos in the chorion during agent administration.

However, Maccubbin taught a method for screening an agent for toxic activity in rainbow trout, which is a teleost that has a chorion. Maccubbin taught administering 4 different carcinogens (agents) in DMSO to 50-100 (claim 46) embryos *within chorions* and detecting toxic effects by monitoring survival (see para bridging pages 279-280). Maccubbin taught that DMSO, given its widely recognized membrane penetration properties, can facilitate the passage of agents across the chorion, facilitating the screening for toxicity of agents by being a noninvasive technique, not requiring removal of the chorion. Maccubbin taught applying this technique to automate screening and for use in other species.

Similarly, Black taught application of chemicals to trout embryos by the method of Maccubbin and establishes while not all chemicals will be most efficiently transported across the chorion (egg shell), this method has advantages such as being noninvasive and has the ability to be automated and reproducible dose-response toxicity data should be readily obtainable (paragraph bridging pages 137-138).

Additionally, Marty *et al* showed the uptake of a variety of chemicals through the chorion of medaka using radiolabeled chemicals.

It would have been obvious at the time of filing to combine the teleost screening methods of Mizzel with the knowledge of Maccubbin, Black or Marty demonstrating that toxicity of compounds can

be tested in teleost embryos with the chorion intact. One of skill in the art would have been motivated to not dechorionate the embryos prior to introducing an agent as it would allow for high throughput, automated and noninvasive screening. Loss of embryos in the dechorionation process would be prevented and time would be saved.

One would have a reasonable expectation of success in applying the screening techniques of Mizzel to embryos within their chorions as it was demonstrated in the art that many agents do cross the chorion to affect the embryo. While the chorion may offer some protection to the embryo, the art has demonstrated the chorion is not a complete barrier.

2) Claims 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mizzel (1997) as applied to claims 42-46 above, and further in view of Terse [1993, Toxicon, 31:913-919].

Mizell taught placing each embryo in a single droplet of medium in a single large Petri dish (page 421, col 2, paragraph 4). Mizell did not teach placing each embryo in a well of a multi-well plate (claim 47) wherein the volume of the wells is 300 microliters or less per well (claim 48).

However, Terse et al. taught screening the toxic activity of various mycotoxin agents using 96-well multi-well plates. As evidenced by the specification, standard 96-well plates have a volume of 300 microliters (see page 88, lines 27-29).

It would have been obvious to one of skill in the art at the time of filing to combine the teachings of Mizell in screening agents for toxicity using teleosts with the teachings of Terse *et al*,. to carry out an in vivo toxin screen using 96-well microtiter plates. One would have been motivated to combine these teachings because multiwell plates provide a more convenient means of separating samples without cross-contamination or loss of sample. Terse *et al.* did not specify a volume in which to place the sample in the well, however, in light of the teachings of Mizell using 250µl droplets and the upper volume limit of the wells being 300 µl, one of skill in the art would have been motivated to use a smaller volume of liquid in

the multi-well plate to avoid spill over from one well to another and to conserve and to work with smaller amounts of potential toxin. It was obvious to one of skill in the art by looking a teleost embryo, that 200 µl would be more than sufficient to envelope the entire teleost.

One would have a reasonable expectation of success in carrying out a screen as taught by Mizzel using 96-well plates as taught by Terse *et al.* because it was standard in the art to carry out screens in 96-well plates and the multi-well plates are made of a material similar to Petri-dishes and serve the same purpose, only with an added benefit.

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio, Ph.D./
Primary Examiner
Art Unit 1632